
A regulatory pathway involving Notch1/beta-catenin/Isl1 determines cardiac progenitor cell fate.

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Authors: Chulan Kwon, Li Qian, Paul Cheng, Vishal Nigam, Joshua Arnold, Deepak Srivastava

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Public Summary:

Scientific Abstract:

Regulation of multipotent cardiac progenitor cell (CPC) expansion and subsequent differentiation into cardiomyocytes, smooth muscle or endothelial cells is a fundamental aspect of basic cardiovascular biology and cardiac regenerative medicine. However, the mechanisms governing these decisions remain unclear. Here, we show that Wnt/beta-catenin signalling, which promotes expansion of CPCs, is negatively regulated by Notch1-mediated control of phosphorylated beta-catenin accumulation within CPCs, and that Notch1 activity in CPCs is required for their differentiation. Notch1 positively, and beta-catenin negatively, regulated expression of the cardiac transcription factors, Isl1, Myocd and Smyd1. Surprisingly, disruption of Isl1, normally expressed transiently in CPCs before their differentiation, resulted in expansion of CPCs in vivo and in an embryonic stem (ES) cell system. Furthermore, Isl1 was required for CPC differentiation into cardiomyocyte and smooth muscle cells, but not endothelial cells. These findings reveal a regulatory network controlling CPC expansion and cell fate that involves unanticipated functions of beta-catenin, Notch1 and Isl1 that may be leveraged for regenerative approaches involving CPCs.

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